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VASOCONSTRICTIVE AND VASODILATIVE SYNDROMES OF THE EXTREMITIES*

Raynaud's phenomena, livedo reticularis, and acrocyanosis are syndromes whose clinical manifestations are due to vasoconstriction and the resultant decrease in dermal circulation. Erythermalgia is a rare syndrome whose clinical manifestations result from vasodilatation and increased dermal circulation. Because of certain similarities, these syndromes are frequently discussed as related entities. A clear understanding of the basic physiologic principles and clinical features of each is necessary for proper differential diagnosis and treatment.

Dynamic variations in the dermal circulation of blood occur in response to the ever-changing physical and emotional stimuli of the environment. Usually these variations pass without notice or are accepted as mild, benign and transient phenomena of obvious cause. Common examples of such are facial blushing and coldness of the extremities due to emotional and physical (cold) stimuli. These changes are accepted as of little or no consequence, not only because of their obvious causation, but equally because of their occurrence within certain limits recognized as "normal" or "physiologic." However, in some individuals, the capacity of the dermal vascular network to constrict and to dilate in response to environmental stimuli exceeds these "normal" limits. Also, some persons have physiologic or pathologic derangements of their dermal circulation which produce persistent but changeable circulatory abnormalities. Either vasoconstrictive or vasodilative phenomena, or both, may occur in an individual. Or these phenomena may be superimposed on a persistent derangement of dermal circulation. This potential range of variability has caused confusion in the differential diagnosis of the many syndromes manifested by extremes of dynamic alteration in dermal blood circulation. An understanding of basic physiology serves to enhance one's comprehension of these syndromes and frequently provides one with a modus operandi in formulating a rational treatment program.

This discussion of the various aberrations of dermal circulation refers to digital arteries and veins and their smaller distal branches, or to blood vessels of this general size but located elsewhere on the extremities or trunk. As the digital arteries branch consecutively into smaller units, they finally reach segments which pierce the cutis from below at a perpendicular angle. These vessels then spread out in a reticular capillary network in the same plane as the skin. The venous counterpart of this network essentially parallels the arterial. Thus, the clinical features caused by dynamic changes in this vascular reticulum depend upon the location of the change (arterial, capillary or venous), the degree of constriction or dilatation and its duration. All these factors determine the volume and rate of blood flow through the dermal vascular network and hence are the basis for the symptoms and physical findings in vasoconstrictive and vasodilative syndromes.

RAYNAUD'S PHENOMENA

The most common dermal vasoconstrictive manifestations are Raynaud's phenomena. These vascular phenomena consist of transient episodes of digital pallor, cyanosis and erythema. *Pallor* is caused by constriction to the point of complete occlusion of the digital arteries. When this occurs the affected digit or digits become waxy, yellowish white owing to *absence of arterial blood flow* through the skin. *Cyanosis* is due to a lesser degree of digital arterial (or smaller branch) constriction resulting in a *slow rate of blood flow*. Because of the resulting slower capillary blood flow, the ratio of nonoxygenated to oxygenated hemoglobin rises, thus causing the bluish discoloration. *Erythema* occurs in some patients as a "rebound phenomenon" after *recovery from an episode of vasoconstriction*. In such a circumstance the previously constricted arteries open more widely than "normal" and the affected digit becomes unusually red and warm, with associated throbbing and tingling due to the excess of oxygenated blood flowing through it.

Raynaud's phenomena occur more or less segmentally in the digits. They tend to terminate at the interphalangeal or metacarpophalangeal

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joints and do not extend proximally past the latter. One, two or three phalanges of one or more digits of one or both hands may be affected. Different phalanges, or combinations of phalanges, can be involved in various episodes. When only a single phalanx is affected it is the distal one. When only two on the same finger are involved they are the distal and middle phalanges. When branches smaller than the digital artery are constricted the changes occur only in the end of the distal phalanx. Raynaud's phenomena may also appear elsewhere on the body, presumably because of constriction of the reticular-perpendicular system of arterioles.

Intermittent attacks of either digital pallor or digital cyanosis must be present in order to make the diagnosis of Raynaud's phenomena. Some patients experience pallor alone, others only cyanosis; some experience both occurring sequentially or on different occasions. By understanding the principles of the rate of blood flow in relation to vasoconstriction, one may comprehend the variable occurrence of pallor and cyanosis. Erythema which follows a period of vasoconstriction may be noted and understood, but it is not a requirement for diagnosis. Thus, various patients experiencing Raynaud's phenomena may note one, two or three of the typical color changes. The various combinations of these are: (1) pallor, (2) cyanosis, (3) pallor and cyanosis, (4) pallor and erythema, (5) cyanosis and erythema and (6) pallor, cyanosis and erythema.

For purposes of classification and diagnosis, one may refer: (1) to Raynaud's phenomena occurring as a primary manifestation and without obvious cause, or (2) to Raynaud's phenomena occurring as a result of or in association with some other disease or syndrome. When Raynaud's phenomena have been present for two years or more in the absence of any obvious cause, the patient may be considered to have *Raynaud's disease.* When some local or systemic disease is present and is apparently a factor in causing episodes of digital vasoconstriction, the latter are referred to as *secondary Raynaud's phenomena.* The validity of the time interval of two years has been confirmed by Hines,[1] who has made an extensive study of Raynaud's phenomena. He found that most diseases, in which Raynaud's phenomena were a manifestation, either became apparent at the onset of the vasoconstrictive episodes or became so within a two-year period.

Raynaud's Disease

Raynaud's disease usually has its onset during the early decades of life (second, third and fourth) but has been known to become manifest as late as the seventh decade. It affects females more frequently than males (4:1). The episodes of digital vasoconstriction* usually are precipitated by exposure to a cold environment and occasionally by emotional stress. In the more severe instances of this syndrome, vasoconstrictive episodes may occur without apparent precipitating cause. Some patients experience the vascular phenomena only if their hands become cold, others if they become generally chilled, and some merely if their face and neck are exposed to cool air. Many patients state that damp cold is particularly provocative. The episodes usually occur less frequently, if at all, during warm weather, but patients who have relatively severe Raynaud's disease may have vasoconstrictive episodes during the summer, particularly on cool evenings. Other known precipitating factors include prolonged grasping of an automobile steering wheel, sewing, or working with the hands and arms elevated. Some patients with Raynaud's disease have manifestations of psychoneurosis, while others are emotionally stable. In general, the severity of Raynaud's disease may be evaluated by the frequency and anatomic extent of the vasoconstrictive episodes, the ease with which the episodes are precipitated, and the presence of secondary complications, as described later.

Patients with Raynaud's disease may experience digital paresthesias, pain, ulceration, infection, or edema in addition to vasoconstrictive episodes. Paresthetic distress is described as coldness, tightness, numbness, pain, burning or tingling. This ordinarily is present only during a vasoconstrictive phase, and disappears with the return of normal circulation. Pain is a feature in patients who develop the typical small areas of dry gangrene on their finger tips. These areas frequently are distinctly uncomfortable, especially when pressure is applied to them. When these small ulcers heal they leave a tiny pitted scar, a diagnostic stigma of Raynaud's phenomena. Paronychial or subungual infection usually occurs only in the more severe forms of this syndrome. When present, infection frequently increases the pain and causes disability by preventing normal use of the involved digit or digits. Slight digital swelling may occur with Raynaud's disease, usually only when it is severe. This swelling is of no significance except that it must be differentiated from the changes of scleroderma.

Physical findings in Raynaud's disease include: (1) the typical episodic color changes of the skin incident to vasoconstriction and (2) trophic changes. The latter may include fingernail deformities, paronychia, subungual infection, loss of fingernail, ulcerations or scars of the finger tip and sclerodactylia. The last-mentioned condition may occur in patients having moderately severe or severe Raynaud's disease of long standing. The physical findings in such an affected digit include atrophy of the skin with loss of normal elasticity, loss of digital hair and the presence of small areas of depigmentation and hyperpigmentation. Sclerodactylia categorically involves only the digits and must be differen-

*Raynaud's phenomena most commonly affect the fingers and toes, particularly the former. Uncommonly, these phenomena may involve the tip of the nose, ear lobe, cheek and tongue.

tiated from acrosclerosis and generalized scleroderma; the latter two syndromes exhibit similar skin changes but involve larger areas. In acrosclerosis these dermal changes affect considerable portions of the extremities: the face, neck and upper anterior part of the thorax; generalized scleroderma is an even more diffuse process involving the skin of most of the body.

In summary, the several criteria of *Raynaud's disease* are: (1) episodes of Raynaud's phenomena which are precipitated by exposure to cold, emotional stress or other causative factors, (2) occurrence of these vasoconstrictive phenomena, usually bilaterally and symmetrically, (3) absence of gangrene except for the characteristic finger-tip type, (4) absence of any underlying primary causative disease and (5) duration of symptoms for two years or more.

Treatment—The treatment of Raynaud's disease may be conservative or surgical depending on various factors, the most important of which is its severity. Surgical therapy (sympathectomy) ordinarily is reserved for the more severe, progressive forms. In the milder, nonprogressive cases, the nature of the condition is explained to the patient. He is assured that extensive gangrene does not occur and the importance of avoiding the known factors that precipitate the vasoconstrictive episodes is emphasized. Certainly the avoidance of these precipitating factors is of the greatest therapeutic importance. Some patients with severe Raynaud's disease are advised to try living in a warm climate. Care is taken to point out that this move should be initially on a trial basis to ascertain whether or not the beneficial effect of a warm climate is worth the sacrifices involved in leaving the home community. Patients with Raynaud's disease may also be advised to cease the use of tobacco for at least six months to determine whether or not the frequency of attacks can be reduced in this way. If no benefit occurs during such a period, the resumption of the use of tobacco may be expected to have no serious effect upon the severity of the disease. Ideally, however, it is well for patients who have a vasoconstrictive disease to avoid the use of nicotine, which has known vasoconstrictive properities.

Psychiatric evaluation is advisable if there are significant manifestations of psychoneurosis.

Vasodilating drugs such as priscoline, dibenzyline and nicotinic acid have been of only minimal benefit in doses that could be tolerated comfortably. The use of a 2 per cent nitroglycerin ointment in an attempt to prevent vasoconstrictive phenomena has been found to be impracticable. The side effects of these drugs frequently have caused so much discomfort that the patients have elected to stop treatment.

In the more severe, progressive forms of Raynaud's disease, particularly when there are secondary trophic manifestations and when conservative treatment has failed to relieve symptoms or prevent progression of the disease, surgical measures may be considered. Bilateral lumbar sympathectomy (removal of the first and second ganglia plus the third, when visible) will almost always relieve patients who have Raynaud's disease of the lower extremities. Unfortunately, sympathectomy for disease of the upper extremities (removal of the stellate and the second, third and fourth thoracic ganglia) benefits only approximately half of the patients operated upon. Presumably, this is due to a more diffuse distribution of the sympathetic nervous pathways in the upper extremity, which makes complete sympathectomy for the upper extremities a technically difficult task. Sympathectomy may prevent or decrease the episodes of vasoconstriction and in that way decreases the pain and assists in the healing of ulceration and in the control of infection. However, it does not give absolute protection against the occurrence of vasoconstrictive attacks or the development of future trophic complications. There is no definite evidence that sympathectomy will alter the course of acrosclerosis or diffuse scleroderma. In Raynaud's disease, it may indirectly deter the development of secondary sclerodactylia by inhibiting episodes of vasoconstriction.

Secondary Raynaud's Phenomena

Raynaud's phenomena that are secondary manifestations of other diseases may occur in a variety of conditions such as rheumatoid arthritis, thromboangiitis obliterans, arteriosclerosis obliterans, thoracic-outlet syndrome, acrosclerosis, cold injury, diseases of the central nervous system (particularly the cervical portion of the spinal cord), ergotism, heavy-metal poisoning, and may also be observed in individuals who habitually use vibrating tools. The criteria for differentiating secondary Raynaud's phenomena from primary Raynaud's disease are as follows:

1. Exposure to a cold environment or to emotional stress may or may not precipitate Raynaud's phenomena when they are secondary to some primary disease.

2. Secondary Raynaud's phenomena are frequently neither bilateral nor symmetrical.

3. Gangrene may be considerably more extensive in secondary Raynaud's phenomena as, for example, in arteriosclerosis obliterans or thromboangiitis obliterans.

4. Frequently the primary underlying disease associated with secondary Raynaud's phenomena is quite obvious.

Treatment—The treatment of secondary Raynaud's phenomena is essentially that of the underlying disease plus the treatment outlined for Raynaud's disease. Sympathectomy is justifiable only when the vasoconstrictive phenomena are severe or when the primary disease warrants such a procedure (for example, thromboangiitis obliterans).

LIVEDO RETICULARIS

Livedo reticularis is characterized by a prominent, reticular (mottling), reddish-blue discolor-

ation of the skin of the extremities. Occasionally it may also occur on the trunk. The vascular aberration in this syndrome is a partial occlusion of the perpendicular arterioles which pierce the cutis from below. The syndrome is due to endothelial proliferation or vasoconstriction, or both, resulting in a decreased rate of blood flow through the reticular capillaries and venules. The reticular distribution of the vessels affected causes the typical pattern of cyanosis.

The symptoms of livedo reticularis include color changes and paresthetic distress. The characteristic color changes usually are intensified upon exposure to cold. Conversely, they may be alleviated partially or completely on exposure to a warm environment. Paresthetic distress may be described by the patient as an aching, heaviness, numbness, tingling or coldness. These symptoms are relatively mild, nondisabling and mainly of nuisance value.

Ulceration in livedo reticularis is very unusual. When it does occur, it appears in an area of marked cyanosis, presumably a region of relative ischemia. These lesions are slow to heal and are seen most commonly in the lower medial portion of the leg, in the so-called "ulcer-bearing area." Some patients say that ulceration appears during cold weather, while a few state that it occurs during the warm summer months.

The physical findings of livedo reticularis include the typical color changes as described and, on rare occasions, ulcerations. The latter are very similar to those of chronic venous insufficiency. Categorically, there are three basic designations of livedo reticularis, namely: (1) cutis marmorata, (2) livedo reticularis idiopathica and (3) livedo reticularis symptomatica.

Cutis marmorata is the mildest form of this syndrome and is described as a bluish mottling that occurs only on exposure to a cold environment. It is seen rather frequently in young girls after they have been exposed to cold water or cold air. The syndrome is transient, uncomplicated and clinically benign. In contrast, *livedo reticularis idiopathica* is more or less persistent and, as the descriptive term indicates, occurs in the absence of any demonstrable underlying disease.

Livedo reticularis symptomatica is the form associated with other dermal disease such as erythema induratum, cutaneous syphilis, periarteritis nodosa, and systemic diseases such as lupus erythematosus.

Treatment—The treatment of livedo reticularis idiopathica is ordinarily quite simple. The patient is assured that the disorder is benign and is of little or no clinical significance. The relationship of a cold environment to worsening of the discoloration is explained, and the advisability of avoiding undue exposure to cold is pointed out. Because of the possibility of ulceration in areas of maximal involvement, the patient is advised to avoid trauma to the skin.

The treatment of a skin ulcer due to livedo reticularis is essentially the same as that for ulcer due to chronic venous insufficiency. This includes cleansing of the ulcer base with bland solutions such as boric acid, applications of lyocyte powder (dried human blood cells), rest in bed, elevation of the limb, and measures aimed at vasodilatation (warm environment, whiskey, vasodilating drugs). In very rare instances, ulcers that have failed to heal with these measures have been treated with skin grafts.

Recently, my colleagues and I have used ganglion-blocking drugs such as hexamethonium and pentolinium in the treatment of livedo reticularis when the severity of the syndrome warranted such treatment. Although these drugs have certain unpleasant side effects, they have seemed to be effective in hastening the healing of ulcers and moderately so in alleviating the cyanosis. We have also used these drugs with reasonable success in forecasting the efficacy of surgical sympathectomy. Other vasodilating drugs, in our experience, have demonstrated little or no beneficial effect.

Sympathetic ganglionectomy is rarely necessary in the treatment of livedo reticularis. My colleagues and I have resorted to it when ulcers have recurred or failed to heal with medical measures. After sympathectomy, the discoloration of livedo reticularis usually decreases in extent and tends to be pink rather than blue.

ACROCYANOSIS

Acrocyanosis is characterized by a persistent, diffuse, bluish discoloration of the hands, feet, or both. The cyanosis does not extend proximal to the wrist or ankle though some patients with acrocyanosis also have an associated livedo reticularis. The etiology and physiology are unknown. Presumably the syndrome is the result of a diffuse vascular aberration that causes a slow rate of blood flow through the skin of the affected extremities. Some investigators have suggested that this is due to arteriolar or capillary constriction, or both; others believe the venules are dilated and tortuous. Which, if either, of these explanations is true, is unknown. Occasionally one may note changing reticular areas of pink color. These are probably due to a temporary "normal" rate of blood flow through the perpendicular-arteriole reticular-capillary network.

Patients with acrocyanosis usually seek medical advice because of the considerable discoloration of their hands or feet. Some patients also complain of having cold extremities. As with other vasoconstrictive syndromes, exposure to a cold environment tends to make acrocyanosis more intense. Examination confirms the facts related by the patient and discloses no other evidence of a vascular, local or systemic disease that might cause cyanosis.

Treatment—There is no specific treatment for acrocyanosis nor are there complications from it. My colleagues and I follow the practice of reassuring the patient as to the benign nature of the syndrome. We suggest avoidance of exposure

to cold and explain the reason for the suggestion. Sympathetic ganglionectomy has not been necessary in our experience with this syndrome except when an associated hyperhidrosis has been disabling.

ERYTHERMALGIA (Erythromelalgia)

Erythermalgia is a descriptive term which designates a very rare, vasodilative syndrome characterized by episodes of redness (ery-), heat (-therm-), and pain (-algia) involving the hands and feet, more often the latter. The etiology of this syndrome is unknown and usually the disease occurs without obvious cause. Occasionally it is associated with polycythemia (*rubra*) vera or hypertension, and it has been reported in instances of gout and organic neurologic disease or heavy-metal poisoning such as from thallium, mercury or arsenic.

The pathophysiology is that of considerable dilatation of the small arteries (for example, the dorsalis pedis and the posterior tibial) and their distal branches. There is a clear relationship between episodes of vasodilatation and the environmental temperature of the patient. Most patients who experience erythermalgia soon learn that exposure to a warm environment precipitates their symptoms. Conversely, exposure to a cool or cold environment promptly abolishes these symptoms. In many patients a critical environmental temperature may be demonstrated; above this temperature typical vasodilative phenomena appear, and below it they do not occur, or if present, do not persist.

The symptoms of erythermalgia seem explainable on a basis of increase in rate and volume of blood flow through the skin of the involved extremities. Certainly the sensations of warmth and throbbing pain, plus the visible erythema, are manifestations of this increase. The severity of symptoms varies; in some patients it may be extreme. My colleagues and I know of one patient who committed suicide presumably because of frequent severe episodes of erythermalgia.

Physical examination discloses no evidence of organic peripheral arterial disease. Observation during an episode of erythermalgia assists greatly in the diagnosis by demonstrating markedly increased warmth and redness of the involved extremities. It also permits evaluation of the severity of the symptoms.

Diagnosis depends upon: (1) a careful evaluation of the history with special attention to the relationship of environmental temperature to the precipitation of the symptoms (it should be clearly understood that the patient is entirely asymptomatic between the acute episodes), (2) the observation of a typical acute episode and (3) the determination of a reasonably consistent critical temperature level. In every instance it is important to exclude specific causative factors and to ascertain whether or not the syndrome is primary (idiopathic) or secondary to some underlying disease.

Treatment—The treatment of erythermalgia is not uniformly successful. The more severe the syndrome the less likely it is that a satisfactory result will be obtained. It is important to determine whether there is a primary cause for the erythermalgia, and to direct treatment at such a cause when it is present. For example, successful treatment of polycythemia vera frequently results in cessation or a decrease in the frequency of attacks of associated erythermalgia.

The basic treatment of primary erythermalgia consists of: (1) the avoidance of an environmental temperature sufficiently warm to provoke an episode, (2) the use of a cold environment (local or general) to bring about cessation of an acute attack, (3) the use of acetylsalicylic acid to alleviate the symptoms and (4) the use of vasoconstrictive drugs as prophylaxis against acute episodes.

The relationship of a warm environment and critical temperature to the precipitation of acute episodes of erythermalgia has been discussed. Obviously, afflicted patients should attempt to avoid an environmental temperature that is sufficiently warm to provoke an attack. Milder forms of the disease may be relatively easily controlled in this manner. However, rigid control of one's environmental temperature so as to avoid "critical" warmth at all times is rarely possible. Thus, this method of control is rarely completely successful, particularly if the disease is severe. Patients may be helped by living in a moderate climate or by the use of air conditioning to control their environmental temperature. Use of open sandals with or without lightweight hose may help to prevent attacks.

During an attack, patients can obtain prompt relief by the local use of cold (immersing affected extremities in cool or cold water, or placing them on a cold object) or by exposing themselves to a cold environment (air-conditioned room, cool outside air). Most patients with erythermalgia discover this fact themselves.

Acetylsalicylic acid in small or average doses (0.65 Gm., one to four times daily) often may be highly successful in preventing acute episodes of erythermalgia. On occasion my colleagues and I have noted relief from symptoms for several days after ingestion of only 0.65 Gm. of this drug at one time. No adequate explanation of this is available, but we have learned to suspect erythermalgia when a patient mentions that marked and prolonged relief of an episodic burning distress in the extremities follows ingestion of acetylsalicylic acid.

Several vasoconstrictive drugs have been used in the treatment of erythermalgia, including epinephrine, norepinephrine, ephedrine and kutapressin (a substance isolated from liver extract). Although an occasional patient may obtain a temporary favorable response to the use of such drugs, it can be said in general that treatment with them is rarely significantly or persistently beneficial. However, it seems reasonable to try vasoconstrictive agents in all cases for the sake of the occasional patient who obtains some relief.

Other forms of treatment that were used in the past, but are rarely, if ever, used at present include radiation therapy, histamine desensitization, administration of antihistamine agents, attempts at desensitization of the skin to warmth and section, crushing or alcohol injection of peripheral nerves supplying the affected extremities.

Prognosis—The prognosis of erythermalgia is essentially favorable. My colleagues and I know of no deaths that could be attributed directly to this syndrome; possibly the suicide mentioned previously might be attributable indirectly to it. Deaths from underlying diseases that may be causing erythermalgia should not be considered due to the erythermalgia itself.

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REFERENCE

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The opinions and conclusions expressed herein are those of the author and do not necessarily represent the official views of the Scientific Council of the American Heart Association.